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A paradigm shift: Combinatorial chemotherapy with simvastatin and metformin for castrate resistant prostate cancer

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Background & Objectives: Treatment of metastatic castrate-resistant prostate cancer (CRPC) has been historically challenging with limited therapeutic success. Docetaxel is considered first-line treatment for metastatic CRPC and provides modest increase in overall survival benefit; however, docetaxel treatment results in frequent occurrence of several severe side effects. Identification of a more effective alternate chemotherapy with fewer side-effects is needed. CRPC cells have increased survival benefit due to higher rate of metabolism with increased expression of 3-hydroxy-3-methylglutaryl-Coenzyme A reductase (HMG-CoAR) and constitutive activation of Akt; loss of adenosine monophosphate-activated protein kinase (AMPK) activity due to decrease in Ser485/491 phosphorylation. Simvastatin (SIM), a potent HMG-CoAR inhibitor and metformin (MET), an AMPK activator were used in combination to investigate potential synergistic inhibition of CRPC growth and survival.

Methods: Castrate-resistant sub-lines of LNCaP, C4-2B3 and B4 were used in the study which demonstrated limited cell viability reduction with docetaxel treatment over pharmacological range. Techniques used were MTT, scratch, transwell invasion, colony formation assays, flow cytometry, Western blot, deuterium incorporation and GC/MS analyses. In vivo efficacy in castrated male nu/nu mice orthotopically inoculated with C4-2B4 cells was demonstrated by oral intake 3.5-7.0 µg/g/day SIM or 175-350 µg/g/day MET alone or in combination, in comparison to 24 µg/g intraperitoneally-injected docetaxel for 9 weeks.

Results: C4-2B3 and C4-2B4 cells treated with 1:500 combinations SIM and MET significantly reduces cell viability, inhibited cell migration, invasion and colony formation. Minimal reduction in viability (<10%) of normal human prostate PrEC cells was noted at highest SIM/MET combination. Compared to SIM and MET alone, combination treatment led to G1-phase cell cycle arrest in both cell lines culminating in cell death by autophagy and secondary necrosis by 48-96 hours of treatment. SIM/MET combination synergistically decreased Akt phosphorylation, increased AMPK activity and decreased HMG-CoAR activity in time-dependent manner. Orthotopic C4-2B4 implantation resulted in tumor formation, cachexia and metastasis to bone. Treatment with either low or high dose SIM/MET combination completely inhibited tumor growth, cachexia and metastasis to bone; prevented PSA failure more effectively than docetaxel, SIM or MET. Docetaxel treatment caused tumor growth inhibition but resulted in severe toxicity and mortality. SIM/MET combination did not demonstrate any apparent toxicity. SIM and MET were bio-available in plasma and prostate tissue.

Conclusions: Combination SIM and MET significantly and synergistically inhibited metastatic CRPC survival both *in vitro* and *in vivo* and may be a promising chemotherapeutic alternative for metastatic CRPC.

Biography

Sanjay Gupta is an Associate Professor & Research Director in the Department of Urology at the Case Western Reserve University and University Hospitals Case Medical Center. He also holds secondary appointments in the Departments of Nutrition and Division of General Medical Sciences at Case Comprehensive Cancer Center. He has obtained Faculty Position in 2002 at Case, School of Medicine.

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